Appendix #1 120-Day Safety Update Report Review

The 120-day Safety Update was sent to the Agency on 12/3/98 and received 12/7/98. The report included post-study surveillance data through July 31, 1998. Pertinent references to this report can be found in the NDA Medical Review Document's safety summaries of the pivotal phase 2 studies, OMC-BUS-3 and OMC-BUS-4. There were no new reports of graft failure or unusual toxicity found within the sponsor's Safety Update. There were 3 additional late deaths related to GVHD reported in the Safety Update of the allogeneic trial, OMC-BUS-4. No new cases of VOD were identified, but there were 3 additional cases of GVHD. This information was included in the NDA Medical Review.

As of the clinical cut-off date for the Safety Update, 39/42 patients treated in OMC-BUS-3 had been observed through BMT Day +100. The median follow-up for the 24 patients who were still disease free at the time of the updated cut-off was 321 days. Fifty of 61 patients on OMC-BUS-4 had been observed through BMT Day +100. The median follow-up for the 38 patients in that study who remained disease free (progression free) at the updated cut-off was 269 days.

A review of the updated number of patients in each study with adverse events reported in the early study time interval – BMT Day –7 to BMT Day +28, revealed that most of the changes were minor and related to the allogeneic study, OMC-BUS-4. Three changes in this early time interval were reported for OMC-BUS-3. The number of patients reporting "Pelvic pain" was increased from one to two (5%), while the number reported having "Pain" decreased by one to 14 (33%). One additional patient was added to the tabulation of those who reported insomnia in this study – 32 (76%). As noted above, 3 additional patients were reported to develop GVHD in the allogeneic study. The remaining adverse events for which additional patients in the allogeneic study were tabulated were all limited to a single additional patient per category: thrombosis, 20 (33%); hypotension, 7 (11%); diarrhea, 51 (84%); protime increased, 1 (2%); creatinine increased, 13 (21%); dyspnea, 15 (25%); pharyngitis, 11 (18%); skin discoloration, 5 (8%); acne, 4 (7%); ear disorder, 2 (3%). There were no additional reports of seizures, hallucinations, delirium, or confusion in either study. Review of the Safety Update Table of Serious Adverse Events and Deaths for the entire observation period up to the new clinical cut-off date, revealed no unusual events or toxicities that were not discussed at length in the course of the medical review document.

To do a similar comparison of the originally submitted safety data and the Safety Update data regarding the observation period beyond BMT Day +28 is hampered by the sponsor's pooling of the two studies' data into one table, Table 9.3.7.20 Summary of 3 and 4 Adverse Events Rated Serious by the Investigator by Body System and COSTART Preferred Term All Patients. However, the only changes in the data from the time interval BMT Day+29 to BMT Day +100 for these events appear limited to an additional SAE "Fever" and a single additional SAE "Interstitial Pneumonitis."

Labeling reflects the information provided in the Safety Update.

Appendix #2 Methodology Employed by Reviewer in the Conduct of the Literature Review

The sponsor has submitted an analysis of the world literature pertaining to the safety and efficacy of high-dose oral busulfan as conditioning therapy for hematopoietic progenitor cell transplantation. The application describes the methodology of the sponsor's literature search as beginning with retrieval of 2552 citations for the keywords "busulfan", "myleran", "transplant", "preparative regimen", and "conditioning regimen". In a subsequent step, non-MEDLINE reference titles (from EMBASE, BIOSIS, IPA, and Derwent Drug File) were reviewed to eliminate articles that were non-European foreign articles or European articles from minor institutions, articles about post-transplant relapses, articles regarding techniques for measuring engraftment and extracorporeal marrow treatment, and most articles published in a foreign language. After this initial elimination process, 910 non-MEDLINE citations and 698 MEDLINE citations remained.

These 1608 abstracts were reviewed and citations referring to review articles, purging, update or follow-up articles, and articles that focused on detection of post-transplant residual disease were eliminated, leaving 602 articles which were reviewed in completion. That review eliminated 25 additional papers, which were found to be review articles or did not actually pertain to busulfan. The sponsor refers to the remaining 577 papers as the "Overall Database", and data from these papers regarding patient number and age, disease type, transplant type, cytoreductive regimens employed, engraftment, relapse, survival, and toxicities were tabulated.

A "Subset Database" was then defined by two selection criteria. Papers from the "Overall Database" were included in this subset if they included a report of time to engraftment and if the paper reported on ≥ 23 patients. Engraftment had been considered a relevant efficacy measurement. Myeloablation was considered as an alternative efficacy measurement, but none of the "Overall Database" papers reported this information, and since engraftment requires myeloablation, engraftment was felt to be a relevant measure of efficacy. (END of Phase 2 MEETING). When these two selection criteria were applied, the sponsor identified 43 articles for inclusion in the "Subset Database".

From a review standpoint the following basic issues regarding the quality of the dataset were identified for exploration:

- Were pertinent papers in the "Overall Database" overlooked and not included in the "Subset Database"?
- Were pertinent publications in the world literature not identified and included in the sponsor's "Overall Database"?
- Was the information abstracted from the 43 articles in the "Subset Database" accurate?

To answer the final question, the reviewer reabstracted the pertinent information from the "Subset Database" articles that had been submitted for review in Volume 1.53 of the application, and compared it to the sponsor's summary data in Tables .

In an effort to answer the first question, the reviewer inspected Appendix 4, the sponsor's tabular Summary Information for the 577 Papers Comprising the "overall Database" in Volume 1.52, and identified all papers that were cited as including ≥ 23 patients – 115 publications. Then, using both the tabular Summary Information and the Reference List of the 577 Summarized Articles found in Appendix 3, Volume 1.52 (which included the article titles in the citations), the reviewer devised criteria that would qualify a paper in those 115 publications for audit by the agency to confirm they did qualify for inclusion in the sponsor's "Subset Database". Those criteria were as follows:

- Article noted by sponsor to not specify the underlying disease.
- Article noted by sponsor to primarily focus on transplantation in a non-malignant disease setting, e.g., thalassemia.
- Article title indicates the focus is on purging.
- Article title indicated the focus is on second transplant.
- Article title indicated that dimethylbusulfan was the conditioning agent.
- Article title that indicated the focus was a specific toxicity, other than hepatic or pulmonary toxicity.
- Articles that have role of supportive care as main focus, e.g. use of growth factors.
- Articles in a foreign language (1).
- Data provided in Letters

64 citations remained after this process of elimination and the reviewer requested the resulting list of articles below from the sponsor for audit. Fifteen titles (**in bold**) suggested that the primary focus was toxicity, but these were selected for review to ensure efficacy data had not been overlooked. The italicized citations were provided by the sponsor within the original application and were not included in the article request. Some citations did not clearly correlate between Appendices 3 and 4, and are noted as such below.

Alexanian, R., 1995. Myeloablative therapy for primary resistant multiple myeloma.

Anderson, J.E., 1996. Unrelated donor marrow transplantation for myelodysplasia and MDS-related acute myeloid leukaemia.

Anderson, J.E., 1996. Allogeneic marrow transplantation for refractory anemia: a comparison of two preparative regimens and analysis of prognostic factors.

Atkinson, K., 1996. (Tabular reference doesn't match a title in Appendix 3. AML-43 + CML-19)

Bandini, G, 1994. Toxicity of high-dose busulphan and cyclophosphamide as conditioning therapy for allogeneic bone marrow transplantation in adults with haematological malignancies. (Article included in submission, Volume 1.54)

Bensinger, W.I., 1996. High-dose therapy followed by autologous hematopoietic stem-cell infusion for patients with multiple myeloma.

Blume, K. G., 1993. A prospective randomized comparison of total body irradiation-etoposide vs. busulfan-cyclophosphamide as preparatory regimens for bone marrow transplantation in patients with leukemia who were not in first remission: a SWOG study.

Brodsky, R., 1990. Frequency of veno-occlusive disease of the liver in bone marrow transplantation with a modified busulfan/cyclophosphamide preparative regimen.

Busca, A., 1997. Unrelated donor or autologous marrow transplantation for treatment of acute leukemia.

Carpenter, P.A., 1996. Allogeneic bone marrow transplantation for children with ALL conditioned with busulfan, cyclophosphamide and melphalan.

Casper, J., 1995. Unrelated bone marrow donor transplants for children with leukemia or myelodysplasia.

Cassileth, P.A., 1997 or 1992 (tables don't match). Escalating the intensity of post-remission therapy improves the outcome in acute myeloid leukemia: the ECOG experience.

Clift, R.A. 1994. (Tables don't match – 43 patients with CML and allogeneic transplant)

Cony-Makhoul, P., 1995. Busulphan and melphalan prior to autologous transplantation for myeloid malignancies.

Copelan, E. A., 1994? (Tables don't match – 65 patients and autologous transplant)

Copelan, E. Al, 1996. Influence of GVH on outcome following allogeneic transplantation with radiation-free preparative therapy in patients with advanced leukemia.

Crilley, P., 1995. Extramedullary toxicity of a conditioning regimen containing busulphan, cyclophosphamide and etoposide in 84 patients undergoing autologous and allogeneic bone marrow transplantation.

De Magalhaes-Silverman, M., 1997. Busulfan and cyclophosphamide as preparative regimen for patients with lymphoma.

Devergie, A., 1995. Allogeneic bone marrow transplantation for CML in first chronic phase: a randomized trial of busulfan-cytoxan vs. cytoxan-total body irradiation as preparative regime: a report from the French Society of Bone Marrow Graft.

Dimopoulos, M., 1993. Thiotepa, busulfan, and cyclophosphamide: a new preparative regimen for autologous marrow or blood stem cell transplantation in high-risk multiple myeloma.

Dix, S.P., 1996. Association of busulfan area under the curve with VOD following BMT. Submitted in Volume 54 and 60.

Essell, J. H., 1992. Marked increase in VOD of the liver associated with methotrexate use for GVHD prophylaxis in patients receiving busulfan/cyclophosphamide.

Ghalie, R. 1994. Busulfan-containing pre-transplant regimens for the treatment of solid tumors.

Hartmann, O., 1997. Peripheral blood stem cell and bone marrow transplantation for solid tumors and lymphomas: Hematologic recovery and costs: A randomized, controlled trial.

Hartsell, W. F., 1995. Pulmonary complications of bone marrow transplantation: a comparison of total body irradiation and cyclophosphamide to busulfan and cyclophosphamide.

Hassan, M., 1991? (Tables don't match – 27 patients)

Huss, R., 1996. Effect of mixed chimerism on GVHD, disease recurrence and survival after HLA-identical marrow transplantation for aplastic anemia or CML.

Jones, R.J., 1990. High-dose cytotoxic therapy and bone marrow transplantation for relapsed Hodgkin's disease.

Keating, S., 1997. Prognostic factors of patients with AML allografted in first complete remission: An analysis of the EORTC-GIMEMA AML 8A trial.

Klein, J. L., 1996? (Tables don't match – 89 patients.)

Linker, C.A., 1993. Autologous bone marrow transplantation for AML using busulfan plus etoposide as a preparative regimen.

Lund, M.B., 1995. Decreased lung function in one year survivors of allogeneic bone marrow transplantation conditioned with high-dose busulphan and cyclophosphamide.

Lynch, M. H., 1995. Phase II study of busulfan, cyclophosphamide and fractionated total body irradiation as a preparatory regimen for allogeneic bone marrow transplantation in patients with advanced myeloid malignancies.

Meresse, V., 1992. Risk factors for hepatic VOD after high-dose busulfan-containing regimens followed by autologous bone marrow transplantation: a study in 136 children. Article included in Volume 1.62.

Michel, G., 1994. Allogeneic bone marrow transplantation for children with acute myeloblastic leukemia in first complete remission: impact of conditioning regimen without total-body irradiation – a report from the Societe Francaise de Greffe de Moelle.

Michel, G., 1997. Late effects of allogeneic bone marrow transplantation for children with acute myeloblastic leukemia in first complete remission: the impact of conditioning regimen without total-body irradiation – a report from the Societe Francaise de Greffe de Moelle. I have this article.

Morgan M., 1991. The toxicity of busulphan and cyclophosphamide as the preparative regimen for bone marrow transplantation.

Nevill, T.J., 1992. Treatment of myelodysplastic syndrome with busulfan-cyclophosphamide conditioning followed by allogeneic BMT.

Nevill, T.J., 1991. Regimen-related toxicity of a busulfan-cyclophosphamide conditioning regimen in 70 patients undergoing allogeneic bone marrow transplantation.

O'Donnell, M.R., 1995. Busulfan/cyclophosphamide as conditioning regimen for allogeneic bone marrow transplantation for myelodysplasia.

Ozkaynak, M. F., 1991. Hepatic VOD post-bone marrow transplantation in children conditioned with busulfan and cyclophosphamide: incidence, risk factors, and clinical outcome.

Petersen, F.B., 1989. Busulfan, cyclophosphamide and fractionated total body irradiation as a preparatory regimen for marrow transplantation in patients with advanced hematological malignancies: a phase I study.

Petersen, F.B., 1993. Autologous marrow transplantation for patients with AML in untreated first relapse or in second complete remission.

Pettengell, R., 1996. Survival benefit from high-dose therapy with autologous blood progenitor-cell transplantation in poor-prognosis non-Hodgkin's lymphoma.

Phillips, G.L., 1991. Busulfan, cyclophosphamide, and melphalan conditioning for autologous bone marrow transplantation in hematologic malignancy.

Przepiorka, D., 1994. Thiotepa, busulfan, and cyclophosphamide as a preparative regimen for marrow transplantation: risk factors for early regimen-related toxicity.

Przepiorka, D., 1997. Allogeneic blood stem cell transplantation in advanced hematologic cancers.

Rapoport, A.P., 1997. Patients greater than or equal to age 40 years undergoing autologous or allogeneic BMT have regimen-related mortality rates and event-free survivals comparable to patients < age 40 years.

Ratanatharathorn, V., 1993. Busulfan-based regimens and allogeneic bone marrow transplantation in patients with myelodysplastic syndromes.

Ravindranath, Y., 1996. Autologous bone marrow transplantation versus intensive consolidation chemotherapy for AML in childhood.

Reiffers, J., 1993? (Tables don't match – 32 patients with CML and autologous BMT)

Reiffers, J., 1994? (Tables don't match – 95 patients with CML and autologous BMT)

Ringden, O., 1996. A comparison of busulphan vs. Total body irradiation combined with cyclophosphamide as conditioning for autograft or allograft bone marrow transplantation in patients with acute leukaemia. Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation.

Rosenthal, M.A., 1994. High dose busulphan/cyclophosphamide for autologous bone marrow transplantation is associated with minimal non-hemopoietic toxicity.

Rozman, C., 1996. Risk factors for hepatic veno-occlusive disease following HLA-identical sibling bone marrow transplants for leukemia.

Shaw, P.J., 1994. Childhood AML: outcome in a single center using chemotherapy and consolidation with busulfan/cyclophosphamide for bone marrow transplantation.

Tutschka, P.J., 1989? (Tables don't match – 90 patients with leukemia and allogeneic BMT)

Tutschka, P.J., 1991? (Tables don't match – 123 patients with leukemia and allogeneic BMT)

Uberti, J.P., 1994. Allogeneic bone marrow transplantation in patients with MDS. Article provided in Volume 1.55.

Vassal, G., 1996? (Tables don't match – 61 pediatric patients with various malignancies and VOD)

Vowels, M.R., 1992. Autologous and allogeneic bone marrow transplantation for childhood acute nonlymphoblastic leukemia.

Vowels, M.R., 1994. Allogeneic and autologous bone marrow transplantation for acute non-lymphoblastic leukaemia.

Weaver, C. H., 1997. Treatment-related mortality in 1000 consecutive patients receiving high-dose chemotherapy and peripheral blood progenitor cell transplantation in community cancer centers.

Woods, W.G., 1993. Intensively timed induction therapy followed by autologous or allogeneic bone marrow transplantation for children with acute myeloid leukemia or MDS: a Children's Cancer Group pilot study.

Finally, in an effort to answer the question of whether pertinent publications from the world literature had been omitted from the "Overall Dataset", the reviewer requested a literature search conducted by the FDA Medical Librarian using the key words "busulfan" and "transplantation", covering the years 1980-1998. The reviewer also conducted her own MEDLINE search using the following search requests: "busulfan and randomized", "busulfan and transplant and engraftment", "busulfan and conditioning regimen", "busulfan and preparative regimen", "busulfan and transplantation". The latter search combination yielded 937 citations. In an effort to narrow the focus of this attempt at verification of the sponsor's search, the reviewer chose to limit her analysis to review of titles from 1990-1998, and to those citations obtained from the "busulfan and randomized" search. The titles and abstracts were evaluated for potential pertinence to the sponsor's review, using the same criteria described earlier:

- Article did not appear to specify the underlying disease.
- Article focus is on transplantation in a non-malignant disease setting, e.g., thalassemia.
- Article focus appears to be on purging.
- Article focus is on second transplant.
- Article is on dimethylbusulfan.
- Article focus is on a specific toxicity other than hepatic or pulmonary toxicity.
- Article has supportive care as main focus, e.g. use of growth factors.

- Article in a foreign language.
- Data provided in Letters or Editorials

Pertinent articles were cross-referenced with Appendices 3 and 4 in Volume 1.52, and if they did not appear were requested for audit. The following 16 articles appeared to have potential relevance after screening using the criteria above, and did not appear in the Volume 1.52 Appendices:

Beinert, T. Eur J Med Res. 1996; 1 (7): 343. Late pulmonary impairment following allogeneic bone marrow transplantation.

Bensinger, WI. Bone Marrow Transplant. 1997 June; 19(12): 1183. High-dose busulfan, melphalan, thiotepa and peripheral blood stem cell infusion for the treatment of metastatic breast cancer.

Bertz, H. Bone Marrow Transplant. 1997 June; 19(12): 1169. Busulfan/cyclophosphamide in volunteer unrelated donor BMT: excellent feasibility and low incidence of treatment-related toxicity.

Copelan, EA. Blood. 1992; 80(7): 1648. Conditioning for allogeneic marrow transplantation in patients with lymphohematopoietic malignancies without the use of total body irradiation.

Fields, K.K. Semin Oncol. 1998 Apr; 25(2 Suppl 4): 1-6. Defining the role of novel high-dose chemotherapy regimens for the treatment of high-risk breast cancer.

Gondo, H. Bone Marrow Transplant. 1997 November; 20(10): 821. Autologous peripheral blood stem cell transplantation for AML.

Harousseau, J.L. Blood. 1997 October; 90(8): 2978. Comparison of autologous bone marrow transplantation and intensive chemotherapy as postremission therapy in adult acute myeloid leukemia. The Groupe Ouest Est Leucemies Aigues Myeloblastiques.

Hartmann, O. Eur J Cancer. 1997 Oct; 33(12):2126-9. Stage IV neuroblastoma in patients over 1 year of age at diagnosis: consolidation of poor responders with combine busulfan, cyclophosphamide and melphalan followed by in vitro mafosfamide-purged autologous bone marrow transplantation.

Ljungman, P. Bone Marrow Transplant. 1997 December; 20(11): 909. High busulfan concentrations are associated with increased transplant-related mortality in allogeneic bone marrow transplant patients.

Majolino, I., 1997 December. Leuk-Lymphoma, 26 (Suppl 1):53-9. Transplantation of unmanipulated allogeneic PBSC: preliminary report on 24 patients.

Pavlovsky, S. Ann Oncol. 1998 Feb; 9(2): 151-7. Autologous peripheral blood progenitor cell transplantation mobilized with high-dose cytarabine in AML in first complete remission.

Schiller, G. Bone Marrow Transplant. 1998 Jan; 21(2): 141-5. Autologous CD34-selected blood progenitor cell transplants for patients with advanced multiple myeloma.

Schultz, KR. Bone Marrow Transplant. 1994;13(6):817. Graft failure in children receiving HLA-mismatched marrow transplants with busulfan-containing regimens.

Slattery, JT. Blood. 1997 Apr 15; 89 (8): 3055. Marrow transplantation for chronic myeloid leukemia: the influence of plasma busulfan levels on the outcome of transplantation.

Slattery, JT. Bone Marrow Transplant. 1995; 16(1): 31. Graft-rejection and toxicity following bone marrow transplantation in relation to busulfan pharmacokinetics.

Sutton, L. Blood. 1996; 88(1): 358. Factors influencing outcome in de novo myelodysplastic syndromes treated by allogeneic bone marrow transplantation: a long-term study of 71 patients Societe Francaise de Greffe de Moelle.

During the process of auditing the literature review it became apparent that an alternative spelling of busulfan was sometimes used in the world literature. A MEDLINE search was conducted with "busulphan and transplantation" to assess for any additional citations such a spelling change may yield. One hundred fifty-one citations were identified. Using the criteria applied to earlier searches, the reviewer found two additional references to add to the audit for the years 1990-1998:

Martin, C. Bone Marrow Transplant. 1998; 21(4): 375. Autologous peripheral blood stem cell transplantation mobilized with G-CSF in AML in first complete remission. Role of intensification therapy in outcome.

Ranson, MR. Br J Haematol. 1991; 79(2): 162. Post consolidation therapy for adult patients with acute myeloid leukaemia.

The 1990-1998 citations from a MEDLINE search using "busulfan and engraftment", "busulfan and preparative regimen", and "busulfan and conditioning regimen" were reviewed using the criteria described earlier. The following 7 additional potentially pertinent articles were identified for audit by the reviewer:

Alegre, A. Bone Marrow Transplant. 1998; 21(2): 133. Autologous peripheral blood stem cell transplantation for multiple myeloma: a report of 259 cases from the Spanish Registry.

Alegre, A. Bone Marrow Transplant. 1997 August; 20(3): 211. Comparison of peripheral blood progenitor cell mobilization in patients with multiple myeloma: high-dose cyclophosphamide plus GM-CSF vs. G-CSF alone.

Copelan, E.A. J Clin Oncol. 1992; 10(2): 237. Radiation-free preparation for allogeneic bone marrow transplantation in adults with acute lymphoblastic leukemia.

Hassan, H.T. Support Care Cancer. 1997 July; 5(4): 299. Factors influencing haematological recovery after allogeneic bone marrow transplantation in leukaemia patients treated with methotrexate-containing GVHD prophylaxis. A single-centre experience.

Kalaycioglu, M. Bone Marrow Transplant. 1995; 15(1): 105. Survival after ABO-incompatible allogeneic bone marrow transplant after a preparative regimen of busulfan and cyclophosphamide.

Schiffman, K. Biol Blood Marrow Transplant. 1997 November; 3(5): 261. High-dose busulfan, melphalan, and thiotepa followed by autologous peripheral blood stem cell transplantation in patients with aggressive lymphoma or relapsed Hodgkin's disease.

Van Besien, K. J Clin Oncol. 1996; 14(11): 3036. Impact of preexisting CNS involvement on the outcome of bone marrow transplantation in adult hematologic malignancies.

It should be noted that the sponsor conducted their final literature search on November 2, 1997. Thirteen of the above 25 articles were published before or during October 1997. Two were published in October. Two were published in November 1997. Half of the articles found through the methodology described above were published after the literature search was conducted.

There were 4 additional articles that appeared to meet criteria for audit, but were already included in Appendices 3 and 4. These were also requested, as the abstracted data in Appendix 4 did not appear to correlate with the citation's abstract narrative. They are listed as follows:

Crawford, SW. Chest. 1992; 101(5): 1257. Predictive value of pulmonary function tests before marrow transplantation.

Dusenbery, KE. Int J Radiat Oncol Bio Phys. 1995; 31(1): 119. Randomized comparison of cyclophosphamide-total body irradiation vs. busulfan-cyclophosphamide conditioning in autologous bone marrow transplantation for acute myeloid leukemia.

Quigley, PM. Pediatr. Pulmonol. 1994; 18(6): 361. The effects of bone marrow transplantation on pulmonary function in children.

Vignetti, M. Bone Marrow Transplant. 1996; 18 Suppl 2: 59. Autologous bone marrow Transplantation in children with AML: report from the Italian National Pediatric Registry.

The FDA Library conducted an independent literature search at the reviewer's request. The reviewer eliminated articles from that search which were selected for review above, or were part of the sponsor's 43 article "Subset Dataset."

The following articles were obtained for review based on the Library literature search. Those articles with an asterisk were submitted in a literature request to the Library.

SciSearch® Cited Ref Sci:

Clift, R. Leukemia. 1992; 6(2): 104. Marrow transplantation in patients with acute myeloid-leukemia.**

Storb, R. Bone Marrow Transplantation. 1990; 6(1): 80. HLA-identical marrow transplantation in the leukemias without t-cell depletion.**

Derwent Drug File:

Stevens, RF. Br. J. Haematol. 1998; 101(1): 130. Marked improvements in outcome with chemotherapy alone in paediatric acute myeloid leukaemia: results of the United Kingdom Medical Research Council's 10th AML trial.

Zander AR. Clin Cancer Res. 1997; 3(12 Pt.2): 2671. High dose chemotherapy with busulfan, cyclophosphamide, and etoposide as conditioning regimen for allogeneic bone marrow transplantation for patients with acute myeloid leukemia in first complete remission.

Giona, F. Br. J. Haematol. 1997; 99(3): 671. ALL R-87 protocol in the treatment of children with acute lymphoblastic leukaemia in early bone marrow relapse.**

Wingard JR. Blood. 1989; 74(4): 1428. Predictors of Death from Chronic GVHD after bone marrow transplantation.**

Goldman JM. N Engl J Med. 1986; 314(4): 202. Bone Marrow Transplantation for Patients with CML.**

BIOSIS Previews:

Schuler, US. Bone Marrow Transplantation. 1998; 22(3): 241. Pharmacokinetics of intravenous busulfan and evaluation of the bioavailability for the oral formulation in conditioning for haematopoietic stem cell transplantation.**

Klein JL. Bone Marrow Transplantation. 1996; 17(4): 479. Bone marrow engraftment following unrelated donor transplantation utilizing busulfan and cyclophosphamide preparatory chemotherapy.**

Brodsky I. Semin Oncol. 1993; 20 (4 Suppl.4): 27. Treatment of CML with allogeneic bone marrow transplantation after preparation with busulfan and cyclophosphamide BUCY2 an update.

Van der Jagt, RH. Bone Marrow Transplant. 1991; 8(3): 211. Busulfan and cyclophosphamide as a preparative regimen for bone marrow transplantation in patients with prior chest radiotherapy. **

Hartman, AR. Bone Marrow Transplantation. 1998; 22(5): 439. Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs. total body irradiation: A meta-analysis.**

PubMed:

Bonin A. Bone Marrow Transplant. 1998; 21(11): 1085. Big BU/CY is associated with a favorable long-term outcome in patients allotransplanted for chronic myelogenous leukemia in chronic phase.**

Van Besien, K. Biol Blood Marrow Transplant. 1997; 3(3): 150. Allogeneic transplantation for recurrent or refractory non-Hodgkin's lymphoma with poor prognostic features after conditioning with thiotepa, busulfan, and cyclophosphamide: experience in 44 consecutive patients.

Appendix #3: Foot Note List of References Associated with the Review

[1] Crilley P. Extramedullary toxicity of a conditioning regimen containing busulphan, cyclophosphamide and etoposide in 84 patients undergoing autologous and allogenic bone marrow tranplantation. Bone Marrow Transplant 15(3): 361-365, 1995.

[2] Kroger N. Busulfan, cyclophosphamide and etoposide as high-dose conditioning therapy in patients with malignanlt lymphoma and prior dose-limiting radiation therapy. Bone Marrow Transplant. 21(12): 1171-1175, 1998.

[3] Bunin, N. Partially matched bone marrow transplantation in patients with myelodysplastic syndromes. JCO 6(12): 1851-1855, 1988.

[4] Weiss, A. A phase 1 study of dimethylacetamide. Cancer Chemotherapy Reports. 16: 477-485, 1962.

[5] Oxman A, Cook D, et al. User' Guides to the Medical Literature: VI. How to Use an Overview. JAMA 272(17), 1994: 1367-1371.

[6] Guyatt g, Sackett D, et al. Users' Guides to the Medical Literature: IX. A Method for Grading Health Care Recommendations. JAMA 272(22): 1800-1804.

[7] Bloomfield DJ. Should Bisphosphonates Be Part of the Standard Therapy of Patients With Multiple Myeloma or Bone Metastases From Other Cancers? An Evidence-Based Review. JCO 16(3), 1998: 1218-1225.

[8] Shaw E. Looking Through the Retrospectoscope in the Era of Evidence-Based Medicine. JCO 15(4), 1997; 1289-1290.

[9] Cassileth P. Chemotherapy Compared with Autologous or Allogeneic Bone Marrow Transplantation in the Management of Acute Myeloid Leukemia in First Remission. NEJM 339(23): 1649-1656.

[10] Dusenbery K. Randomized Comparison of Cyclophosphamide-Total Body Irradiation Versus Busulfan-Cyclophosphamide Conditioning in Autologous Bone Marrow Transplantation for Acute Myeloid Leukemia. Int. J. Radiation Oncology Biol. Phys 31(1):119-128, 1995.

[11] Christiansen, N. Allogeneic Bone Marrow Transplantation for the Treatment of Adult Acute Leukemias. Hematology/Oncology Clinics of North America 7(1):177-200, 1993.

[12] Reiffers J. Comparison of Allogeneic or Autologous Bone Marrow Transplantation and Chemotherapy in patients with Acute Myeloid Leukaemia in First Remission: A Prospective Controlled Trial. British J. of Haematology 72:57-63, 1989.

[13] Mayer, R. Intensive Postremission Chemotherapy in Adults with Acute Myeloid Leukemia. NEJM 331(14): 896-903, 1994.

[14] Stevens R. Marked Improvements in Outcome with Chemotherapy Alone in Paediatric Acute Meyeloid Leukemia: Results of the United Kingdom Medical Research Council's 10th AML Trial. British J. Heamatology 101: 130-140, 1998.

[15] Weick J. Randomized Investigation of High-Dose Versus Standard-Dose Cytosine Arabinoside with Daunoraubicin in Patients with Previously Untreated Acute Myeloid Leukemia: A SWOG Study. Blood 88(8): 2841-2851, 1996.

[16] Storb, F. HLA-identical marrow transplantation in the leukemia's without T-cell depletion. Bone Marrow Transplantation 6(Suppl 1):80-84, 1990.

[17] Copelan EA. Conditioning for Allogeneic Marrow Transplantation in Patients with Lymphohematopoietic Malignancies without the Use of Total Body Irradiation. Blood 80(7): 1648-1658, 1992.

[18] Clift R. Marrow Transplantation in Patients with Acute Myeloid Leukemia. Leukemia 6(Suppl 2): 104-109, 1992.

[19] Chronic Myeloid Leukemia, in *Hematology Basic Principles and Practice*, ed. Hoffman, Benz, Shattil, Furie, Cohen, Silberstein. Second Edition, 1995.

[20] Lee S. Initial Therapy for Chronic Myelogenous Leukemia: Playing the Odds. JCO, 16(9): 2897-2903, 1998.

[21] Gale R. Survival with Bone Marrow Transplantation versus Hydroxyurea or Interferon for Chronic Myelogenous Leukemia. Blood 91(5):1810-1819, 1998.

[22] Clift R. Treatment of Chronic Myeloid Leukemia by Marrow Transplantation. Blood 82(7): 1954-1956, 1993.

[23] Applebaum F. Bone Marrow Transplantation for CML. Seminars in Oncology 22(4):405-411, 1995.

[24] Hehlmann R. Randomized Comparison of Interferon-α with Busulfan and Hydroxyurea in Chronic Myelogenous Leukemia. Blood, 84(12): 4064-4077, 1994.

[25] Sebban C. Allogeneic Bone Marrow Transplantation in Adult Acute Lymphoblastic Leukemia in First Complete Remission: a Comparative Study. JCO, 12(12): 2580-2587, 1994.

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